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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
HOLLERAN, A	
ART UNIT	**PAPER NUMBER**
1642	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/640,838	Applicant(s) SINN ET AL.	
	Examiner Anne Holleran	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,5 and 14-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5 and 14-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/817,185* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The preliminary amendment filed 8/16/2000 (Paper No. 4) is acknowledged.

Claims 1-3 and 6-13 were canceled.

Claim 4, 5 and 14 remain of the originally filed claims.

Claims 14- 42 (renumbered as claims 15-43, 37 CFR 1.126) were added. Thus, claims 4, 5 and 14-43 are pending and examined on the merits. For purposes of examination, any dependencies on claims 15-43 have been adjusted to the new claim numbering. However, applicant is required to submit an amendment to correct the dependencies.

Claim Rejections - 35 USC § 112

2. Claims 14, 20, 21, 22, 30, 37, and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 provides for the use of a conjugate, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 14 is also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for

example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 14 is also indefinite for depending from canceled claims.

Claim 20 is indefinite for reciting "wherein the conjugate comprises 4-aminophyenylsulphonic acid or 4-aminophenylphosphonic acid linked to albumin, a azo group being present". From the description of preferred embodiments of the claimed invention it appears that 4-aminophyenylsulphonic acid or 4-aminophenylphosphonic acid are parts of a linker between a chemotherapeutic drug and a protein. Furthermore, the azo group does not link the 4-aminophyenylsulphonic acid or 4-aminophenylphosphonic acid to the albumin. Therefore, it appears that to more clearly define the claimed invention, the claim should recite "wherein the *linker further comprises* 4-aminophyenylsulphonic acid or 4-aminophenylphosphonic", because claim 20 depends from claim 15, which already limits the claimed invention by reciting that the linker comprises an azo group; and because the moieties 4-aminophyenylsulphonic acid or 4-aminophenylphosphonic do not appear to be contemplated as active substances, but as part of a linker.

Claims 21 and 22 are indefinite for reciting " a linker containing an azo group being present". Claims 21 and 22 depend from claim 15, which already limits the claimed invention by reciting that the linker comprises an azo group.

Claim 30 is indefinite because it appears to broaden the scope of claim 23, from which it depends by reciting that the binding comprises the formation of an ester.

Claim 37 is indefinite because of the recitation of active substances that appear from the specification to be part of linker structures.

Claim 43 is indefinite for reciting "a derivative of phenylene". The specification fails to adequately describe the scope of derivatives of phenylene. A derivative may be interpreted as reading on one atom derived from a phenylene.

3. Claim 43 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The basis for this rejection is that the disclosure of a linker comprising a phenylene is not adequate to describe the full scope of the linkers that are "derivatives of phenylene". Because the scope of the term "derivative" includes fragments, fragments that may be as small as one atom of a phenylene molecule, the multitude of structures encompassed by the phrase "derivatives of phenylene" is large, and the disclosure of a linker that comprises phenylene is not representative of the genus of linkers encompassed by claim 43. Thus, the conjugates of claim 43 are not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 4, 15-18, 23-27, 30, 35, 36, 37, 42 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Marquardt et al (U.S. Patent 4,731,439; issued 03/15/1988).

Claim 15 is drawn to a conjugate comprising an active substance, a native human protein and a linker linking the active substance and the native human protein, wherein the linker can be cleaved intracellularly and wherein the linker comprises an azo group. Claim 16 further limits by limiting the active substance to a chemotherapeutic agent or to a photoactive compound. Claim 4, further limits claim 16 in that the chemotherapeutic agent is an antibiotic. Claim 17 further limits in that several active substances useful for treating a disease are linked to said protein through one or more linkers. Claims 18, 26 and 27, further limit the linkers of claim 15, 16 and 17, respectively, in that the liner comprises –Y-R-N=N-, where Y is C(O), $S(O)_2$, P(O)OH or As(O)OH, and R is an aromatic compound. Claim 23 is drawn to a process of preparing the conjugate of claim 15 comprising binding an active substance to a native human protein by means of a liner containing an azo group. Claim 30, depending from claim 23, recites that the binding comprises the formation of a chemical bond that is either an azo group or an ester. Claim 24 is drawn to a method of treating a disease, tumoral, infectious, or autoimmune, comprising administering the conjugate of claim 15. Claim 25 further limits claim 16 in that several active substances are present. In claim 35, dependent from claim 15, the active substance

comprises an acid group; in claim 36 the acid group may be a $-CO_2H$, $-SO_3H$, $-PO_3H_2$, or $-AsO_3H_2$. In claim 37, the active substance may be an aminobenzoic acid. However, in view of the specification, claim 37 is also interpreted to include conjugates where the linker comprises an aminobenzoic acid. Claims 42 and 43, dependent from either claim 18, 26 or 27, limit the aromatic group to comprising a phenylene or a derivative of a phenylene.

Marquardt teaches a conjugate comprising a toxic peptide (a snake venom growth arresting peptide) and a member of a specific binding pair (see claim 1), where the member of the specific binding pair may be a low-density lipoprotein, a growth factor or an immunoglobulin. The immunoglobulin may be human (see col. 4, lines 40-49). Marquardt teaches that the linkage may comprise an azo bond (see claim 6), such as diazobenzoic acid (see col. 4, lines 15-27). Therefore, Marquardt teaches a conjugate comprising a linker where the linker comprises an acid or where the linker comprises –Y-R-N=N- (for diazobenzoic acid, which comprises $-CO_2H$, Y is C(O)). The snake venom is a cytotoxic agent that is useful in treating tumors and pathogenic organisms (col. 5, lines 56-62). Thus, the active agent of Marquardt may be interpreted to be an antibiotic. Marquardt also teaches the linkage of multiple cytotoxic agents to the specific binding member (col. 5, lines 1-12). Thus, Marquardt teaches the conjugates and methods that are the same as that claimed.

5. Claims 23 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Blair and Ghose (Blair, A.H. and Ghose, T.I., Journal of Immunological Methods, 59: 129-143, 1983).

Claims 23-30 are drawn to methods of preparing a conjugate comprising binding an active substance to a native human protein by means of a linker comprising an azo group.

Blair and Ghose teach methods of linking cytotoxic agents to immunoglobulins for targeting agents to cancer cells (see page 129), where the linker comprises an azo bond (see Table I and page 133-134). Thus, Blair and Ghose teach methods that are the same as that claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 15-17, 19, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marquardt (supra) in view of Sivam et al (U.S. Patent 5,116,944; issued 5/26/1992).

Claims 15-17, 19, 28 and 29 are drawn to conjugates wherein the native human protein is human serum albumin. Marquardt fails to teach conjugates comprising human serum albumin. However, human serum albumin is known in the art as a drug carrier intermediate, as a targeting agent and as a stabilizing agent, as evidenced by the teachings of Sivam (col.3, lines 5-29). Sivam also teaches the use of human serum albumin in conjugates comprising a monoclonal antibody and a protein toxin (col. 11, line 4- col. 13, line 12). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the conjugates of Marquardt to include conjugates comprising human serum albumin.

One would have been motivated by the advantages of using human serum albumin in conjugates as taught by Sivam.

7. Claims 4, 5, 15, 16, 21, 22, 31, 32, 33, 34, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blair and Ghose (supra) in view of Sivam et al (supra), in view of Clark et al (U.S. Patent 5,169,934; issued 12/8/1992), and further in view of Sezaki et al. (Critical Reviews in Therapeutic Drug Carrier Systems, 1(1): 1-38, 1984).

Claims 15 and 16 are interpreted to read on conjugates comprising active agents that may be a chemotherapeutic agent that is an antimetabolite or an antibiotic, may be a nucleoside such as cytidine, deoxyuridine, doexycytidine, cytosine arbinoside, 5-flurouracil, 5-fluodeoxuridine, azidothymidine, or an antibiotic such as tetracycline, an antimetabolite such as methotrexate or sulfonamide (claims 4, 5, 21, 22, 31, 32, 33, 34, and 38).

Blair and Ghose generally teach the concept of linkage of cytotoxic agents to immunoglobulins for targeting agents to target sites, and teach that techniques for binding low molecular weight chemotherapeutic agents to immunoglobulins are derived from teachings of how to bind haptens to macromolecular carriers (see page 129, 1st paragraph). Blair and Ghose also teach how to make a linker comprising an azo bond (see Table I and page 133-134). Sivam teaches the use of human serum albumin as a drug carrier that is part of a conjugate. Clark teaches delivery of agents such as doxorubicin (adriamycin), antifungal agents, enzyme inhibitors (read as an example of an antimetabolite) as part of conjugates that comprise cleavable linkers. Sezaki teaches various examples of macromolecule-drug conjugates (see Table 1) that include protein carriers such as albumin and antibodies, and drugs such as cytosine arabinoside

and 5-fluorodeoxyridine (see page 19). Sezaki also teaches the concept of using a linker that may be designed to readily cleavable (see page 6). Thus, it would have been prima facie obvious to one of ordinary skill in the art to have combined the teachings of Blair and Ghose with those of Sivam, Clark and Sezaki to make the conjugates as broadly claimed. Chemotherapeutic agents such as cytidine, tetracycline, methotrexate and sulfonamide are known in the art as useful agents for treatment of either cancer or bacterial infections.

8. Claims 15, 16, 39, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oseroff et al (Oseroff, A.R. et al. Proc. Natl. Acad. Sci., USA, 83(22): 8744-8748; abstract only), in view of Sivam and further in view of Blair and Ghose (supra).

Claims 15, 16 are interpreted to read on conjugates comprising active agents that are photoactive agents. Claims 39 and 40 recite examples of photoactive agents.

Oseroff teaches a conjugate comprising chlorin e6 (an example of a porphyrin, see attached Registry database printout). Oseroff's conjugate comprises a monoclonal antibody and Oseroff does not teach that the antibody is a human antibody. However, the use of human proteins such as human serum albumin for targeting drugs is known in the art as evidenced by the teachings of Sivam (col.3, lines 5-29). Oseroff also fails to teach a conjugate comprising a linker comprising an azo bond. However, such linkers are known in the art, as well as there advantages and the fact that diazo linkers are intracellularly cleavable, as evidenced by the teachings of Blair and Ghose (see Table I and page 133-134). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made

a conjugate comprising a photoactive agent such as chlorin e6 with human serum albumin and a linker comprising an azo bond.

9. Claims 15, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blair and Ghose (supra) in view of Ades et al (U.S. Patent 4,522,750; 06/11/1985).

Claims 15 and 41 are interpreted to read on conjugates comprising active agents and human proteins such as transferrin, where the agents are bound to the protein by a linker comprising an azo bond.

Blair and Ghose teach the binding of active agents to proteins by the formation of an azo linkage (see Table I and page 133-134). Blair and Ghose do not teach the use of transferrin as the carrier protein. However, Ades teaches the benefits of using transferrin for targeting active agents to cells possessing the transferrin receptor (see col. 1, lines 20-31, and col. 7, lines 20-37). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a conjugate comprising a linker with an azo bond and a carrier protein that is human transferrin.

Double Patenting

10. Claims 4, 5 and 14-43 of this application conflict with claims 4, 5 and 14-43 of Application No. 09/641,026. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the

conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

11. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

12. Claims 4, 5, and 14-43 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 4, 5, and 14-43 of copending Application No. 09/641,026. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

AH

Anne L. Holleran
Patent Examiner
September 29, 2001

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